Polyoxalate nanoparticles as new biodegradable and non-inflammatory drug delivery systems

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Statement of Purpose: Biodegradable polymers have been widely employed as drug vehicles including poly(glycolic acid), poly(lactide-co-glycolide) and polycaprolactone. However, there are great needs for the development of new biodegradable drug carriers for the treatment of many inflammatory diseases. In this study, we introduce a new biodegradable and non-inflammatory polyoxalate and report the potential polyoxalate nanoparticles as a drug delivery system for the treatment of acute inflammatory diseases.

Methods: Polymerization. 1,4-cyclohexanedimethanol (16.6 mmol) was dissolved in 14 mL of dry dichloromethane (DCM), under nitrogen, to which triethylamine (43 mmol) was added dropwise at 4°C. Oxalyl chloride (16.6 mmol) in 4 mL of dry DCM was added to the mixture dropwise at 4°C. The reaction was kept under nitrogen atmosphere at room temperature overnight, quenched with a saturated brine solution, and extracted with additional DCM. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The obtained polymer was isolated by precipitation in cold hexane.

Particle preparation. Fifty milligrams of polymers dissolved in 500 μL of DCM was added to 5mL of 10 (w/v)% poly(vinyl alcohol) solution. The mixture was sonicated using a sonicator (Fisher Scientific, Sonic Dismembrator 500) for 30 seconds and homogenized (PRO Scientific, PRO 200) for 1 minute to form a fine oil/water emulsion. The emulsion was added into 20 mL PVA (1w/w%) solution and homogenized for 1 min. The remaining solvent was removed by rapid stirring for at least 3 h. Nanoparticles were obtained by centrifuging at 11,000*g* for 5 min at 4°C, washing with deionized water twice and lyophilizing the recovered pellet.

Physicochemical characterization. Hydrolysis kinetics of polyoxalate was studied by grinding the polymers into fine powders and measuring their molecular weight by a gel permeation chromatography. Drug loading capacity and loading efficiency of polyoxalate nanoparticles were determined by a spectrofluorometer using rhodamine as a model drug. The morphology and size of polyoxalate nanoparticles were observed by a scanning electron microscopy. The cytotoxicity of polyoxalate nanoparticles was investigated using RAW 264.7 cells by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) reduction assay. The cytotoxicity of polyoxalate nanoparticles was compared with that of PLGA nanoparticles.

Results: Polyoxalate synthesized from a one step reaction of oxalic chloride and cyclohexanedimethanol had a molecule weight of 11,000Da with a polydispersity of 1.8. The chemical structure of this polymer was confirmed by NMR analysis. Polyoxalate is expected to readily degrade by water hydrolysis into oxalic acid and the monomeric compound, 1,4-cyclohexanedimethanol, which can be easily removed from a body. The hydrolysis kinetics of polyoxalate was determined by measuring the molecular weight of fine polymer powder under aqueous conditions. It was determined that the half-life of polyoxalate was 6.5 days at pH 7.0. We prepared polyoxalate nanoparticles by an emulsion/solvent displacement method. Polyoxalate nanoparticles were round spheres with smooth surface, with an average diameter of ~ 600 nm. Rhodamine encapsulation efficiency was determined to be 12% by a fluorospectrometer. The cytotoxicity of polyoxalate nanoparticles was evaluated by an MTT method. Polyoxalate nanoparticles exhibited a higher cell viability than PLGA, demonstrating a minimal toxicity of polyoxalate nanoparticles. Confocal fluorescent imaging revealed that rhodamine-loaded polyoxalate nanoparticles were readily phagocytosed by RAW 264.7 cells.

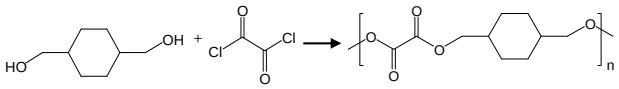

Figure 1. Synthesis and chemical structure of polyoxalate

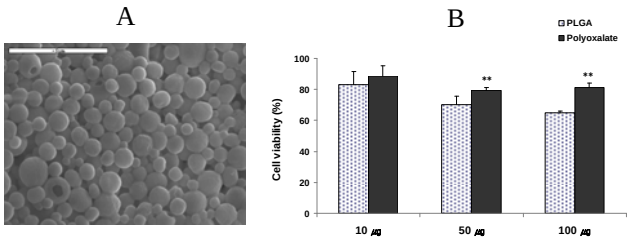

Figure 2. A SEM image of polyoxalate nanoparticles (A) and viability of RAW 264.7 cells treated with PLGA and polyoxalate nanoparticles (B). ** P<0.05.

Conclusions. We synthesized a new biodegradable polyoxalate from a reaction of cyclohexanedimethanol and oxalic chloride. Polyoxalate undergoes water hydrolysis and degrade into non-toxic compounds, which can be easily removed from a body. The hydrophobic polyoxalate was formulated into nanoparticles with smooth surface. Polyoxalate nanoparticles showed a higher cell viability than PLGA nanoparticles. We anticipated that the ease of synthesis and nontoxic degradation products of polyoxalate make them highly potent for numerous applications in drug delivery.

References:

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